STIC-ILL

From: Hunt, Jennifer
Sent: Sunday, November 04, 2001 12:29 PM
To: STIC-ILL
Subject: References for 09/218,481

Please send me the following references ASAP:

JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, (1998 Aug) 18 (8) 887-95

Adv. Exp. Med. Biol. (1998), 454(Oxygen Transport to Tissue XX), 311-317

BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1998 Sep 18) 60 (1) 89-97

JOURNAL OF APPLIED PHYSIOLOGY, (1998 Jul) 85 (1) 53-7

STROKE, (1997 Oct) 28 (10) 2039-44

NEUROSURGERY, (JUN 1997) Vol. 40, No. 6, pp. 1269-1277

NEUROSURGERY, (1997 May) 40 (5) 1016-26

JOURNAL OF CLINICAL INVESTIGATION, (1996 Sep 15) 98 (6) 1400-8

JOURNAL OF NEUROSURGERY, (1996 Dec) 85 (6) 1095-101

Proc Annu Meet Am Assoc Cancer Res, (1996). Vol. 37, pp. A399

Oncology Reports, (1995) 2/6 (1147-1149)

NEUROSURGERY, (1994 Sep) 35 (3) 439-48

YALE JOURNAL OF BIOLOGY AND MEDICINE, (1993 Jul-Aug) 66 (4) 277-314

MOLECULAR BIOLOGY OF THE CELL, (1993 Jan) 4 (1) 121-33

Endothelial Cell Dysfunct. (1992), 477-503

J CELL BIOL. (1990) 111 (5 PART 2), 227A.

Thanks,

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TGFβ II receptor (induced 3-fold), lipocortin-1 (induced 3-fold) a marker for apoptosis in the mammary gland, and neuroligin-1 (repressed 8.75-fold in 1/5 and not detectable in 4/5 regressing tumors).

#2721 Monday, April 22, 1996, 8:00–12:00, Poster Section 12

SU101, a potent inhibitor of PDGF-mediated signaling, inhibits growth of a wide variety of tumor types *in vivo*. Shawver LK, Schwartz DP, Taylorson LT, Longhi MP, Jacobs JS, Powell TJ, and Hirth KP. *SUGEN, Inc., Redwood City, CA 94063.*

Platelet-derived growth factor (PDGF) is one of several growth factors that have been implicated in the unregulated growth of numerous types of cancers. Studies finding concurrent expression of PDGF ligands and receptors as well as studies using dominant-negative mutant receptors have provided a rationale for the design of antineoplastic agents that inhibit PDGF-mediated signaling. SU101 is a small molecule drug which was shown to inhibit PDGF-mediated receptor phosphorylation, DNA synthesis and cell cycle progression. Therefore, it was tested against the C6 glioma cell line which has been shown to be dependent on PDGF receptor function. SU101 was shown to potently inhibit the growth of C6 cells *in vitro* with an IC50 of 0.2 μM. Using a subcutaneous xenograft model in athymic mice, SU101 inhibited the growth of C6 cells in a dose dependent manner. At 20 mg/kg/day, SU101 inhibited the *in vivo* growth of C6 cells >90%. SU101 was then tested on a variety of tumor cell types *in vitro* and *in vivo*. Significant inhibition of tumor growth was observed for some glioma, ovarian, prostate, melanoma, leukemia, and lung tumor cell lines. This provided a rationale for studies in humans and SU101 is currently in Phase I trials.

#2722 Monday, April 22, 1996, 8:00–12:00, Poster Section 13

Expression and testing of recombinant mammastatin. *Ervin PR., Wicha MS., **Biotherapies Incorporated, Ann Arbor, Michigan, 48108, University of Michigan, Ann Arbor, Michigan, 48109*

Factors which influence the growth of mammary epithelial cells may be important for the development of breast cancer. Mammastatin has been identified as a protein that inhibits the growth of normal and transformed human mammary cells. Recent studies have demonstrated that mammastatin is not produced as an active, inhibitory molecule in breast cancers. Furthermore, preliminary evidence suggests that mammastatin levels are lower than normal in breast cancer patients. Mammastatin has recently been cloned and expressed as a recombinant protein in eukaryotic expression systems. Mammastatin was cloned by peptide sequencing, and degenerate, oligonucleotide screening of a normal human mammary epithelial cell cDNA library. A 2.4 kB cDNA clone was identified that recognizes mRNA expressed in normal human mammary cells and in carcinoma cells that produce mammastatin. This cDNA clone is unique but shares sequence homology with both p53 and pRB genes. The mammastatin clone codes for active, immunoreactive mammastatin by *in vitro* transcription and translation assays. Mammastatin has also been expressed in Cos -7 cells. Production of active, inhibitory mammastatin by recombinant methods allows larger quantities of mammastatin to be purified. Availability of recombinant mammastatin will enable further characterization of this molecule and *in vivo* trials of mammastatin for the control of breast cancer.

#2723 Tuesday, April 23, 1996, 8:00–12:00, Poster Section 4

Comparative effects of discodermolide and paclitaxel on induction of apoptosis and perturbation of the cell cycle in various tumor cell lines. Longley, R.E., Gunasekera, S.P., Poulin, S., Day, B.W.*, Hamel, E.* and Hurst, J.+ *Harbor Branch Oceanographic Inst., Ft. Pierce, FL 34946, *Dept. Environ. & Occup. Health, Univ. Pittsburgh, Pittsburgh, PA 15238, *Nat. Cancer Inst., Nat. Inst. Health, Bethesda, MD 20892 and +Goodwin Institute for Cancer Research, Plantation, FL 33313.*

The effects of discodermolide, a microtubule-interactive, marine sponge-derived polyhydroxylated alkatetraene (ter Haar et al., *Biochemistry*, in press), on perturbation of the cell cycle and induction of apoptosis in various tumor cell lines was investigated. GI-101A human breast adenocarcinoma, A549 human lung adenocarcinoma, Jurkat human leukemia and P388 murine leukemia cells were treated with 100 nM and 10 nM of discodermolide or paclitaxel for 24 and 48 hr. Discodermolide (10 nM) increased the percentage of cells in G_2/M phase of the cell cycle and induced appreciable apoptosis in GI-101A and A549 but not Jurkat or P388 leukemia cells following 24 hr incubation. Higher concentrations (100 nM) resulted in a further increase in percentage of cells in G_2/M with a corresponding loss of cells in G_1 and increased cellular necrosis. Similar results were obtained with paclitaxel. Extended 48 hr incubations of GI-101A and A549 cells with 10 and 100 nM discodermolide resulted in high percentages of cells undergoing necrosis, however, Jurkat and P388 leukemia cells still retained apoptotic cell populations. These results indicate that discodermolide and paclitaxel share a similar mechanism of action relating to their specific in vitro activity directed towards cell lines derived from solid tumors vs leukemias.

#2724 Monday, April 22, 1996, 8:00–12:00, Poster Section 13

Preliminary analysis of betulinic acid in human tumor primary cultures. Nagourney, R.A., Su, Y.Z., Makalinao, A.J, Ciarolla, A. and Evans, S.S. *University of California, Irvine and Rational Therapeutics, Long Beach CA 90807.*

Betulinic acid (BA) is a pentacyclic tri-terpene which has shown activity in human melanoma(mel)cell lines (Nat. Med 1:1046,'95). We examined the activity of BA in fresh specimens of human cancer; 3 Mel, 1 AML; 2 NSCLC; 1 Breast; 1 Gastric & 1 B-cell Lymphoma, using the DISC assay, which has been shown to correlate with response and survival in human cancers (JNCI 83:1418'91) and to correlate with molecular markers of apoptosis (AACR 35:1861,'94, AACR 36:66,'95) RESULTS:

(N)	AVG Ic 50 +/− SEM	Median Ic50	Range (ug/ml)
9	12.6 +/− 2.3	10	3.9–24.8

Defining sensitivity, in vitro, as Ic50 ≤ median value for all 9 studies, we found activity in 1/3 Mel; 1/2 NSCLC; 1/1 AML; 1/1 Breast; 0/1 NHL & 1/1 Gastric cancers. Correlation coefficients (Pearson) for CDDP, Doxorubicin (Dox), Nitrogen Mustard, Vp16 & Taxol revealed BA to correlate only with Dox r = 0.858 (pl < .05) CONCLUSIONS: i) BA reveals evidence of cytotoxicity in human tumors @ Ic50's similar to cell line studies ii) The correlation with Dox alone may provide useful insights into BA's mode of action iii) The activity of BA that we have identified in the primary culture DISC assay and that previously reported (Nat Med 1:1046'95) yet its reported inactivity in L-1210 screens (J. Pharm Sci 63:'74), if confirmed, may reflect the superiority of robust apoptotic endpoints for drug screening and discovery. Studies are ongoing to further characterize the activity spectrum for BA.

#2725 Tuesday, April 23, 1996, 8:00–12:00, Poster Section 4

Methionine analogs inhibit cell proliferation and growth of human xenografted gliomas. Poirson, F., Lopez, R., Monneret, C., Dutrillaux, B., Poupon, M.F. *UMR 147-CNRS et URA 1387-CNRS, Institut Curie, 26 rue d'Ulm, 75231 Paris, France.*

MET dependency of human xenografted gliomas was evaluated and an experimental therapeutic approach using MET deprivation or MET analogs to aggravate the altered MET metabolism was designed. Proliferation of 7 human glioma cell lines tested was inhibited in MET^-HCY^- medium, and was poorly or not reversed by HCY addition. Ethionine (ETH) and trifluoromethylhomocysteine (TFH) (concentration range: 0.005–2 mg/ml) inhibited proliferation of all cell lines tested. MET analog-induced inhibition was abolished by MET and enhanced by HCY. In MET^- medium, cells were arrested in the S-phase after 30 h; this blockage was partially reversed by HCY. ETH induced an accumulation of cells in the G_2-phase and apoptosis was observed. ATP was reduced by MET analogs in HCY^+ medium, suggesting complementary effects of MET analogs and HCY. When nude mice bearing human gliomas were fed a synthetic amino-acid mixture (MET^-HCY^+) for 3 weeks, limited but significant growth inhibition (GI) of 40% ($P < 0.05$) was observed. Antitumor effects of 200 mg/kg of ETH alone (46% GI, $P < 0.05$) were potentiated by MET^-HCY^+ diet when co-administered to glioma-bearing mice (77% GI, $P < 0.05$). In conclusion, MET deprivation or MET-analog retarded the growth of human gliomas, and enhanced their respective effects. Therapeutic approaches based on aggravating the MET-metabolism defect of gliomas should be explored, as these cancers are known to be highly resistant to conventional treatments.

#2726 Monday, April 22, 1996, 8:00–12:00, Poster Section 13

Activity of camptothecin analogue (SN-38) in drug resistant human myeloma cell lines. Gleason-Guzman M.C., Foley N.E., Jones S.A., Dalton W.S. *Arizona Cancer Center, University of Arizona, Tucson, AZ 85724*

Drug resistance remains the most significant problem in improving therapy in multiple myeloma. The development of new drugs with novel mechanisms of activity are needed to improve overall outcome. Camptothecins represent a new group of drugs with a unique mechanism of action: poisoning DNA topoisomerase I. SN-38 is believed to be the most potent compound in this class of drugs. The activity of SN-38 was studied in a series of human myeloma cell lines with well characterized mechanisms of resistance. These cell lines include: (1) 8226/DOX, a MDR1/P-gp positive cell line; (2) 8226/DOX · V, a Topoisomerase II mediated resistant line; (3) 8226/MR4 and MR20, LRP positive cell lines; and (4) 8226/LR5, a melphalan resistant cell line mediated by increased glutathione and GST activity. SN-38 was active in the MDR1/P-gp positive cell lines, but cross-resistance was seen in all other cell lines.

Cell Line:	DOX6	DOX1V	MR4	MR20	LR5
Degree of Resistance:	1.1 +/− 0.2	3.0 +/− 0.6	4.8 +/− 1.0	9.6 +/− 2.2	5.0

(mean+/−SD, n = 4 expts.)

There was no difference between the various cell lines for (a) cell doubling time, (b) level of Topo I by immunoblot assay; or (c) catalytic activity of Topo I. We conclude that SN-38 is active in MDR1 resistant cell lines but cross-resistance is observed for cell lines with various mechanisms of resistance, not related to Topo I level or activity.